B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins.

Please cancel claims 28 and 29.

Remarks

The Interview

Applicants and the undersigned greatly appreciate the opportunity to discuss this case with the examiner. The foregoing amendments to the claims are made in response to the discussion with the examiner. For example, the claims have been amended to delete any reference to "therapy", "pathogen" or "treatment of disease", and to refer to the cells in a patient to be killed. By so doing, it was agreed that applicants did not have to demonstrate a therapeutic efficacy, only that the claimed method was effective in killing the targeted cells. The limitations of claims 4 and 25 have been incorporated into claim 1 and claims 4 and 25 cancelled. Claim 26 was also cancelled as duplicative. Claims 5 and 6 were amended to properly depend from claim 1. Claim 27 was amended to properly characterize and limit the claimed Markush group.

Rejection Under 35 U.S.C. § 112, first and second paragraphs

Claims 1-4, 14-18, 25-26, and 28-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the

claimed invention and lack of written description. Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

As discussed at the interview, the primary issue was the question of therapeutic efficacy, not whether or not the method is effective at killing cells. Indeed, this is amply demonstrated by the examples. The secondary issue is the breadth of the claims. As the examiner noted, this can be met by a showing that more than one species of antigen, indicative of the breadth of the genus, can be targeted using the CTLs to kill cells having the antigens on their surfaces.

As discussed at the interview, the application contains a number of specific examples of antigens. See, for example, pages 17-18. As briefly described at pages 39-41 (more details are provided in the examples beginning at page 42), and shown by the data in Figures 1 and 2, an antigen can be an antigen such as mdm-2, presented by a virus-induced tumor cell, RMA (see page 44, lines 12 and 13). Mdm-2 is a normal cellular protein which is expressed at abnormally high levels in tumours (see page 7, line 5). The antigen can also be a viral antigen (example 2, page 52) or a tumor antigen (pages 17-18). The RMA cells were killed in mice. Figure 3 shows the data for CTL mediated killing where the CTLs are specific for an mdm 100 peptide present on tumor cells (this peptide is derived from the mdm-2 protein that is a self protein overexpressed in tumors); Figure 4 shows the data for killing of melanoma cells by CTLs targeted to the mdm100 peptide. See also Figure 6. Page 41, page 57, line 26 to page 58, line12 and Figure 7 shows the data for CTL mediated killing of cells having on their surface HLA-A0201-binding cyclin D1 peptide (101-110), which is derived from the cyclin-D1 protein that is

overexpressed in tumours but also expressed in normal cells . This data is particularly striking because it shows one can kill a cell presenting what would otherwise not be an antigen (i.e., a normal protein) on the surface of the targeted cells IF the antigen is presented within the context of a mismatched HLA. In this example, CTLs with the specified characteristics were made to a selected antigen, in this case cyclin D1, which is known to be overexpressed in a variety of tumours (see page 7, line 4)]

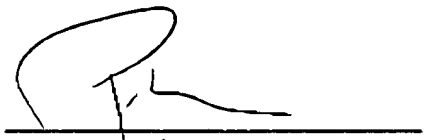
This data shows that the method was effective to kill tumor cells but not normal cells where the CTLs were targeted to normal proteins that were overexpressed in tumor cells. Accordingly, it is believed that applicants have demonstrated the general applicability of the claimed method.

Since the application was filed, the inventor has made CTLs using the protocol described in the application against proteins such as WT1, CD45 and CD68 that are present at higher levels in tumours but also found in normal cells]

The claims have been amended as discussed at the interview to use language the examiner thought was clear and supported. The undersigned would greatly appreciate a call to work out any further required changes in language to place the case in condition for allowance.

Allowance of claims 1-3, 5-18, and 27 is respectfully solicited.

Respectfully submitted,



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U.S.S.N. 09/101,413
Filed: August 7, 1998
MARKED UP VERSION OF AMENDED CLAIMS
PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Five times amended) A method of killing cells in a patient [characterized by expression by the patient of an abnormal antigen or an abnormally elevated amount of a antigen as compared to the non-diseased state, or by expression of an infectious agent protein], the method comprising

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs have a different HLA class I complex (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion <u>on the cells to be killed</u> of [the] <u>(a) an</u> abnormal antigen or <u>(b)</u> antigen which is abnormally elevated in <u>the patient</u> [patients with the disease] or <u>(c)</u> [the] <u>an</u> infectious agent protein <u>antigen</u>, when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed, wherein the HLA class I complex (or equivalent) type presenting the peptide in the cells to be killed is not present in the CTLs to be administered to the patient, and

the CTLs kill the presenting cells.

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

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Please cancel claim 4.

5. (Three amended) A method according to Claim [4] 1 wherein the [polypeptide] antigen is a mutant polypeptide associated with the [diseased] cells to be killed.

6. (Three amended) A method according to Claim [4] 1 wherein the [polypeptide] antigen is present at an abnormally elevated amount in the [diseased] cells to be killed compared to [non-diseased] other cells.

7. (twice Amended) A method according to Claim 1 wherein the [disease is a] cells to be killed are cancer cells.

8. A method according to Claim 7 wherein the cancer is any one of breast cancer; bladder cancer; lung cancer; prostrate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

9. (twice Amended) A method according to Claim 1 wherein the [disease is caused by] cells to be killed have a chronic viral infection.

10. (amended) A method according to Claim 9 wherein the virus is selected from the group consisting of HIV, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

11. A method according to Claim 10 wherein the virus is HIV.

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12. (twice Amended) A method according to Claim 1 wherein the [disease is] cells to be killed are associated with an abnormally elevated amount of a hormone.

13. (twice Amended) A method according to Claim 1 wherein the [disease is a bacterial disease caused by] cells to be killed have a chronic bacterial infection.

14. (Amended) A method according to Claim 1 further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15. (Amended) A method according to Claim 14 wherein the type is determined using DNA typing.

16. (Amended) A method according to Claim 1 wherein the patient is human.

17. (twice Amended) A method according to Claim 14 wherein the cytotoxic T lymphocyte is selected from a library of CTL clones, the library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each CTL clone recognises the [diseased] cells to be killed.

18. (twice Amended) A method according to Claim 17 wherein each CTL clone recognizes at least part of the same molecule contained in or associated with the [diseased] cells to be killed.

Please cancel claims 25 and 26.

27.(Three times amended) A method according to Claim 1 wherein the [molecule] antigen is selected from the group consisting of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-

R, insulin-like growth factor receptor, Met, myc, a p53, BCL-2, [mutant p53,] a polypeptide associated with the BCR/ABL translocation in CML and ALL, [mutant] a CSF-1 receptor, [mutant] an APC, [mutant] a RET, [mutant] an EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins.

Please cancel claims 28 and 29.